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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,622	03/29/2006	Tomi Jarvinen	06267.0126	8385

22852 7590 10/19/2009

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EXAMINER	
STOCKTON, LAURA LYNNE	
ART UNIT	PAPER NUMBER
1626	

MAIL DATE	DELIVERY MODE
10/19/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,622	JARVINEN ET AL.	
	Examiner	Art Unit	
	Laura L. Stockton	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4 and 7-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4 and 7-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 4 and 7-10 are pending in the application.

Rejections made in the previous Office Action that do not appear below have been overcome by Applicant's amendments to the claims. Therefore, arguments pertaining to these rejections will not be addressed.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ

645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 4 and 7-10 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, 6, 8, 14 and 16-24 of U.S. Patent No. 6,313,311. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claimed compound is generically claimed in the patent.

The indiscriminate selection of "some" among "many" is *prima facie* obvious, *In re Lemin*, 141 USPQ 814 (1964). The motivation to make the claimed compounds derives from the expectation that structurally similar

compounds would possess similar activity (e.g., treating hypertension).

One skilled in the art would thus be motivated to prepare products embraced by the patent to arrive at the instant claimed products with the expectation of obtaining additional beneficial products which would be useful in treating, for example, hypertension. The instant claimed invention would have been suggested to one skilled in the art and therefore, the instant claimed invention would have been obvious to one skilled in the art.

Response to Arguments

Applicant's arguments filed June 22, 2009 have been fully considered but they are not persuasive. Applicant argues that the specification may not used as prior art when considering whether the invention defined in a claim of an application would have been an

obvious variation of the invention defined in the claim of a patent and cites M.P.E.P. § 804.

In response, M.P.E.P. § 804 states the following:

When considering whether the invention defined in a claim of an application would have been an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art. *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1279, 23 USPQ2d 1839, 1846 (Fed. Cir. 1992). This does not mean that one is precluded from all use of the patent disclosure.

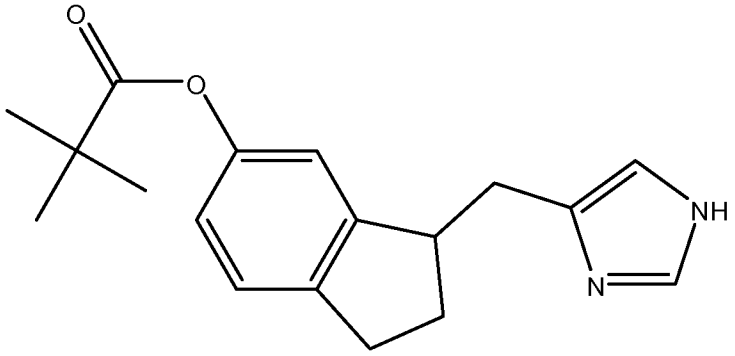
The specification can be used as a dictionary to learn the meaning of a term in the patent claim. *Toro Co. v. White Consol. Indus., Inc.*, 199 F.3d 1295, 1299, 53 USPQ2d 1065, 1067 (Fed. Cir. 1999)("[W]ords in patent claims are given their ordinary meaning in the usage of the field of the invention, unless the text of the patent makes clear that a word was used with a special meaning."); *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1250, 48 USPQ2d 1117, 1122 (Fed. Cir. 1998) ("Where there are several common meanings for a claim term, the patent disclosure serves to point away from the improper meanings and toward the proper meanings."). See also MPEP § 2111.01. Further, those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent. *In re Vogel*, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970). The court in *Vogel* recognized "that it is most difficult, if not meaningless, to try to say what is or is not an obvious variation of a claim," but that one can judge whether or not the invention claimed in an application is an obvious variation of an embodiment disclosed in the patent which provides support for the patent claim. According to the court, one must first "determine how much of the patent disclosure pertains to the invention claimed in the patent" because only "[t]his portion of the specification supports the patent claims and may be considered." The court pointed out that "this use of the disclosure is not in contravention of the cases forbidding its use as prior art, nor is it applying the patent as a reference under 35 U.S.C. 103, since only the disclosure of the invention claimed in the patent may be examined."

Contrary to Applicant's argument, M.P.E.P. § 804 does state that one is not precluded from all use of the patent disclosure and indicates that the specification can be used for purposes such as a dictionary to learn the meaning of a term in the patent claim. Therefore, Applicant's argument is not persuasive.

Applicant argues that the instant claimed prodrug does not fall within the broad genus claimed in U.S. Pat. 6,313,311 because R_6, R_7 and R_8 cannot be ester groups let alone the pivaloyl group {$-C(=O)C(CH_3)_3$} presently claimed.

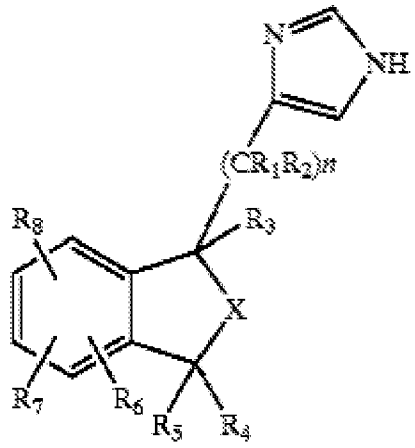
In response, Applicant claims the prodrug, 4-[6-(2,2-dimethylpropanoyloxy)indan-1-ylmethyl]-1H-imidazole, which structure is reproduced below.

4-[6-(2,2-dimethylpropanoyloxy)indan-1-ylmethyl]-1H-imidazole



Claim 1 in U.S. Pat. 6,313,311 claims the compounds of the following formula I

1. An imidazole compound of formula I



or a pharmaceutically acceptable ester or salt thereof.

The instant claimed prodrug is embraced by claim 1 of U.S. Pat. 6,313,311 when it is a pharmaceutically acceptable ester of an imidazole compound of formula I wherein

m is zero;

n is 1;

X is $-CHR_9$;

$\mathbf{R_1}$, $\mathbf{R_2}$, $\mathbf{R_3}$, $\mathbf{R_4}$, $\mathbf{R_5}$, $\mathbf{R_7}$, $\mathbf{R_8}$ and $\mathbf{R_9}$ are each hydrogen; and

R_6 is a hydroxy attached to the 6-position of the indane ring.

See also, for example, claim 5 in the patent (reproduced below)

> **5**. The compound according to claim **1**, wherein n=1 and m=0.

claim 8 in the patent (reproduced below)

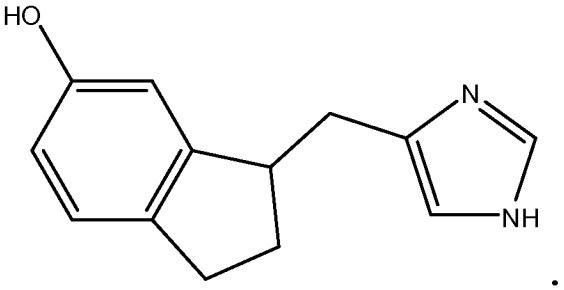
> **8**. The compound according to claim **5**, wherein R_6 is hydroxy at position 4 or 6 of the indane ring and R_7 and R_8 are hydrogen.

and claim 16 in the patent (reproduced below)

> **16**. The compound according to claim **1**, which is 3-(1H-imidazol-4-ylmethyl)-indan-5-ol or a pharmaceutically acceptable ester or salt thereof.

which structural depiction is represented as follows

3-(1H-imidazol-4-ylmethyl)-indan-5-ol



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The disclosure in U.S. Pat. 6,313,311 was used, as allowed by M.P.E.P. § 804, to define "the esters" of an imidazole compound of formula I. On lines 44-46 in column 3 of U.S. Pat. 6,313,311, it states the following:

> salts with alkali metals and alkaline earth metals. Typical esters include the lower alkyl esters, such as the methyl, ethyl and propyl esters.

On lines 1-4 in column 2 of U.S. Pat. 6,313,311 (reproduced below), it states that the alkyl can be branched.

> 2
>
> erably it is chlorine or fluorine. The C_1–C_4-alkyl, C_1–C_4-alkoxy and C_2–C_4-alkenyl etc. groups may be branched or straight chain groups. C_3–C_7-Cycloalkyl is a saturated cyclic hydrocarbon group having preferably 3 to 5 carbon atoms. Optionally substituted amino is an amino group which is

As stated in Bundgaard {**No. 2** – A Textbook of Drug Design and Development, Harwood Academic Publishers, 1991, Chapter 5, pages 113-191}, ester prodrugs of hydroxyl functions are popular (see page 153, section 5.3.2). On page 154 of Bundgaard (reproduced below), the general ester structure {i.e., -OC(=O)R} is shown

which is formed from a hydroxy functional group of a pharmaceutically active compound. The R can represent the alkyl portion of the alkyl ester.

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Table 5.5 Prodrug forms of various functional groups in drug substances.

Functional group	Prodrug form	
-OH	-OOCR	Esters

Further, an alkyl ester wherein the alkyl is a branched alkyl, such as a 2,2-dimethylpropane as found in the instant claimed prodrug, is clearly envisioned by the patented claims. Therefore, esters of an imidazole compound of formula I claimed in the claims in the patent, in light of the definitions in the disclosure of the patent of "the esters of an imidazole compound of formula I" and "alkyl", would lead one skilled in the art to the instant claimed prodrug. Therefore, Applicant's arguments are not persuasive.

Claims 7 and 8 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 15, 16, 19-24 and 27-32 of copending Application No. 11/641,953 {US 2007/0185181}. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application claims methods of using imidazole compounds which generically embrace the imidazole compound being used in the instant claimed method of use.

The indiscriminate selection of "some" among "many" is *prima facie* obvious, *In re Lemin*, 141 USPQ 814 (1964). The motivation to make the compounds for the instant claimed methods of use derives from the expectation that structurally similar compounds would possess similar activity (e.g., treating hypotension).

One skilled in the art would thus be motivated to prepare products embraced by the copending application to arrive at the instant products for the instant

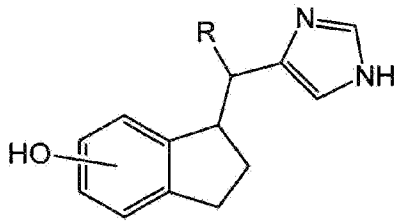
claimed method of use with the expectation of obtaining additional beneficial products which would be useful in treating, for example, hypotension. The instant claimed invention would have been suggested to one skilled in the art and therefore, the instant claimed invention would have been obvious to one skilled in the art.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Applicant's arguments filed June 22, 2009 have been fully considered but they are not persuasive.
Applicant argues that the instant claimed invention is not embraced by the claims in the copending application because there is no possibility for an ester on the phenyl ring of the indane ring.

In response, the copending application claims a method for treating a mammal by administering an imidazole derivative of formula I (reproduced below)



(I)

wherein R is hydrogen or methyl, or a pharmaceutically acceptable ester or salt thereof .

The instant claimed invention of instant claim 7 is embraced by the claims in the copending application when the imidazole derivative is in the form of a pharmaceutically acceptable ester, R is hydrogen and the hydroxy group is attached at the 6-position of the indane ring. As stated above, in the ester form of a compound of formula I in the copending application the hydrogen of the hydroxy group would be replaced with a -C(=O)R wherein R would represent an organic radical such as an alkyl. Therefore, Applicant's argument is not persuasive.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

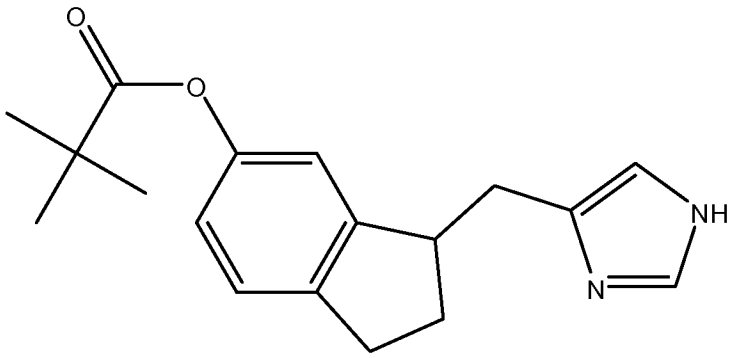
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4 and 7-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Karjalainen et al. {WO 97/12874} and Karjalainen et al. {U.S. Pat. 6,313,311}, each taken alone, or each of the aforementioned Karjalainen et al. references in view of Huhtala et al. {WO 01/051472}, Bundgaard {**No. 1 -** Drugs of the Future, 1991, 16(5), pages 443-458}, Aungst et al. {U.S. Pat. 4,673,679} and Bundgaard {**No. 2** – A Textbook of Drug Design and Development, Harwood Academic Publishers, 1991, Chapter 5, pages 113-191}.

Determination of the scope and content of the prior art (MPEP §2141.01)

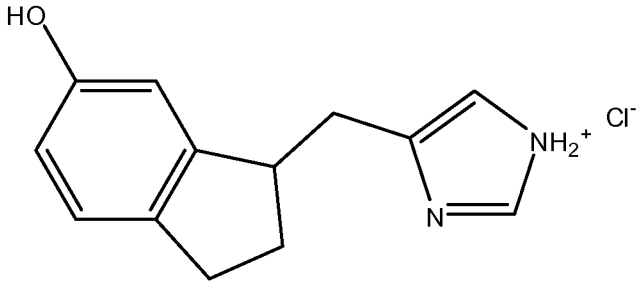
Applicant claims a specific prodrug, 4-[6-(2,2-dimethylpropanoyloxy)indan-1-ylmethyl]-1H-imidazole, which structure is reproduced below,

4-[6-(2,2-dimethylpropanoyloxy)indan-1-ylmethyl]-1H-imidazole



of a known pharmaceutically active hydroxy containing imidazole compound known as MPV-2426 (reproduced below)

4-(6-hydroxyindan-1-ylmethyl)-1H-imidazol-1-ium chloride



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Karjalainen et al. '874 (see entire document; particularly pages 1-4, 11 and 12; and especially Example 15 on page 30) and **Karjalainen et al. '311** (see entire document; particularly columns 1-3, 10 and 11;

and especially Example 15 in column 21) each teach imidazole compounds that are structurally similar to the instant claimed compound.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the compounds of the Karjalainen et al. references and the compound/prodrug instantly claimed is that the instant claimed compound/prodrug is generically described, and claimed, in each of the Karjalainen et al. references as a pharmaceutically acceptable ester.

Huhtala et al. (page 8, last full paragraph) teach the interchangeability of esters of aliphatic and aromatic alcohols {i.e., the -C(=O)R group in instant formula (I)}. Huhtala et al. state that the -OH functionality forms esters with pharmaceutically acceptable acids which are conventional in the field of pharmaceuticals and retain the pharmacological properties of the free form.

Bundgaard (**No. 1**) teaches the advantages of ester prodrugs and why one skilled in the art would be motivated to prepare such ester prodrugs (see entire document; particularly page 444, first column, first full paragraph through to the second column under "Ester prodrugs").

Aungst et al. (column 1, lines 40-48; column 3, lines 1-20; and column 5, lines 20-27, 35-55 and 65-67) and **Bundgaard** (**No. 2** - see the reverse process in Scheme 5.13 at the at the top of page 151; page 153; Table 5.5 on page 154; and page 156) each teach the preparation of a prodrug from a hydroxy containing active ingredient using the process taught in Huhtala et al. of the -OH functionality reacting with a pharmaceutically acceptable acid.

Finding of prima facie obviousness--rational and motivation (MPEP §2142-2413)

The indiscriminate selection of "some" among "many" is *prima facie* obvious, *In re Lemin*, 141 USPQ 814 (1964). The motivation to make the claimed

compound/prodrug of the Karjalainen et al. references derives from the expectation that structurally similar compounds would possess similar activity (e.g., treating glaucoma).

One skilled in the art would thus be motivated to prepare a compound/prodrug embraced by the Karjalainen et al. references, especially in view of the teachings in Huhtala et al., Bundgaard (**No. 1**), Aungst et al. and Bundgaard (**No. 2**), to arrive at the instant claimed compound/prodrug with the expectation of obtaining an additional beneficial compound/prodrug which would be useful in treating, for example, glaucoma, psychiatric and cognition disorders, etc. Absent a factual side-by-side showing of unexpected, unobvious and beneficial results in a comparison study of the instant claimed compound over the compounds in the cited prior art, the instant claimed invention would have been suggested to one skilled in the art and therefore, the instant

claimed invention would have been obvious to one skilled in the art.

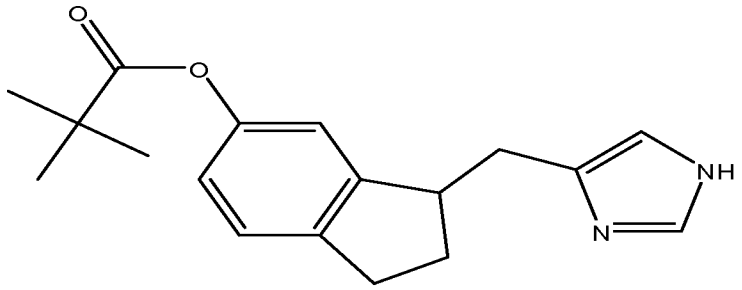
Response to Arguments

Applicant's arguments filed June 22, 2009 have been fully considered but they are not persuasive. Applicant argues that a *prima facie* case of obviousness has not been established of the instant claimed invention over either of the Karjalainen et al. references, each taken alone, or each in view of Huhtala et al. Applicant has argued that: (1) the instant claimed compound/prodrug is not a member of the expressed genus of either of the Karjalainen et al. references because the R_6, R_7 and R_8 variables in the Karjalainen et al. references are not specifically defined to include an ester group; (2) not one of the specific compounds disclosed in the Karjalainen et al. references has an ester functional group and therefore, Karjalainen et al. teach away from the instant claimed compound; and (3) Huhtala et al. do

not specifically point out a pivaloyl group appended to any of the free hydroxyl groups and therefore, Huhtala et al. provide no more guidance to one of skill in the art to modify the generic compounds of Karjalainen et al. to arrive at the instant claimed compound/prodrug.

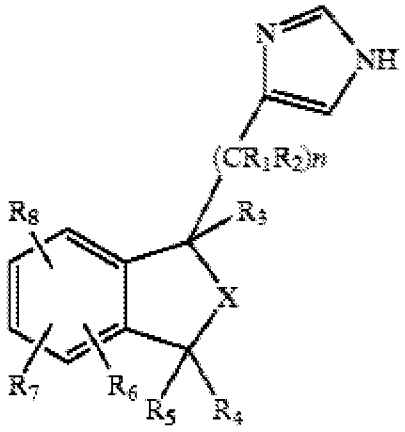
All of Applicant's arguments have been considered but have not been found persuasive. Applicant claims the prodrug, 4-[6-(2,2-dimethylpropanoyloxy)indan-1-ylmethyl]-1H-imidazole, which structure is reproduced below.

4-[6-(2,2-dimethylpropanoyloxy)indan-1-ylmethyl]-1H-imidazole



Karjalainen et al. '311 teach the compounds of the following formula I

The imidazole derivatives of the invention are either compounds of formula I



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or a pharmaceutically acceptable ester or salt thereof.

The instant claimed compound/prodrug is embraced by Karjalainen et al. '311 when it is a pharmaceutically acceptable ester of an imidazole compound of formula I wherein

m is zero;

n is 1;

X is $-CHR_9$;

$\mathbf{R_1}$, $\mathbf{R_2}$, $\mathbf{R_3}$, $\mathbf{R_4}$, $\mathbf{R_5}$, $\mathbf{R_7}$, $\mathbf{R_8}$ and $\mathbf{R_9}$ are each hydrogen; and

$\mathbf{R_6}$ is a hydroxy attached to the 6-position of the

indane ring.

Karjalainen et al. '311 teach the preferred embodiment in column 3, lines 1-2 (reproduced below),

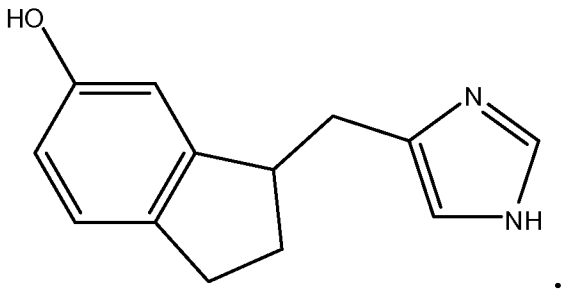
> Especially preferably R_6 is hydroxy at the position 4 or 6 of the indane ring and R_7 and R_8 are hydrogen or R_6 is hydroxy .

Karjalainen et al. '311 disclose Example 15 in column 21 (reproduced below),

> **EXAMPLE 15**
>
> **3-(1H-Imidazol-4-ylmethyl)-indan-5-ol**

which structural depiction is represented as follows

3-(1H-imidazol-4-ylmethyl)-indan-5-ol



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Karjalainen et al. '311 defines "the esters" of an imidazole compound of formula I on lines 44-46 in column 3 where it states the following:

salts with alkali metals and alkaline earth metals. Typical esters include the lower alkyl esters, such as the methyl, ethyl and propyl esters.

On lines 1-4 in column 2 of Karjalainen et al. '311 (reproduced below), it states that the alkyl can be branched.

2

erably it is chlorine or fluorine. The C_1–C_4-alkyl, C_1–C_4-alkoxy and C_2–C_4-alkenyl etc. groups may be branched or straight chain groups. C_3–C_7-Cycloalkyl is a saturated cyclic hydrocarbon group having preferably 3 to 5 carbon atoms. Optionally substituted amino is an amino group which is

As stated in Bundgaard {**No. 2** – A Textbook of Drug Design and Development, Harwood Academic Publishers, 1991, Chapter 5, pages 113-191}, ester prodrugs of hydroxyl functions are popular (see page 153, section 5.3.2). On page 154 of Bundgaard (reproduced below), the general ester structure {i.e., -OC(=O)R} of a prodrug is shown which is formed from a hydroxy functional group of a pharmaceutically active compound. The R represents the alkyl portion of the alkyl ester.

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Table 5.5 Prodrug forms of various functional groups in drug substances.

Functional group	Prodrug form	
-OH	-OOCR	Esters

Further, an alkyl ester wherein the alkyl is a branched alkyl, such as a 2,2-dimethylpropane as found in the instant claimed compound/prodrug, is clearly envisioned by Karjalainen et al. '311. Therefore, the teachings in Karjalainen et al. '311 would lead one skilled in the art to the instant claimed compound/prodrug.

Applicant argues that not one of the specific compounds disclosed in Karjalainen et al. has an ester functional group and therefore, Karjalainen et al. teach away from the instant claimed compound. In response, it is well established that consideration of a reference is not limited to the preferred embodiments or working examples, but extends to the entire disclosure for what it fairly teaches, when viewed in

light of the admitted knowledge in the art, to person of ordinary skill in the art. *In re Boe*, 148 USPQ 507, 510 (CCPA 1966). Further, Applicant argues the decision in *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007). In response, the section in the MPEP 2141.02 (VI) deals with references that may "teach away" but also states that alternative embodiments should not be confused with "teaching away" citing a recent decision, *In re Fulton* (73 USPQ2d 1141). Note the following passage in Fulton at 1146: *"The prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed in the '198 application. Indeed, in the case cited by appellants, In re Gurley, we held that the invention claimed in the patent application was unpatentable based primarily on a prior art reference that disclosed two alternatives,*

one of which was the claimed alternative. Accordingly, mere disclosure of alternative designs does not teach away".

Applicant argues that Huhtala et al. do not specifically point out a pivaloyl group appended to any of the free hydroxyl groups and therefore, Huhtala et al. provide no more guidance to one of skill in the art to modify the generic compounds of Karjalainen et al. '311 to arrive at the instant claimed compound. In response, Huhtala et al. was cited to show that the hydroxy (i.e., -OH) functionality forms esters with pharmaceutically acceptable acids which are conventional in the field of pharmaceuticals and retain the pharmacological properties of the free form. Therefore, it is disagreed that Huhtala et al. do not provide guidance as to how one skilled in the art would make the esters of -OH containing pharmaceutically active compounds.

Applicant argues that: (1) Aungst et al., Bundgaard No. 1 and Bundgaard No. 2 fail to compensate for the deficiences in the Karjalainen et al. references because they fail to provide a reason to modify the compounds in Karjalainen et al. references; (2) Aungst et al., Bundgaard No. 1 and Bundgaard No. 2 teach away from Huhtala et al. {WO '472} because Huhtala et al. do not consider any potential ester derivatives to be prodrugs; (3) Aungst et al. disclose that the pivaloyl group is less effective as a prodrug group; and (4) Aungst et al. and the Bundgaard documents highlight the unpredictability of selecting a suitable prodrug.

All of Applicant's arguments have been considered but have not been found persuasive. It is disagreed that Aungst et al., Bundgaard No. 1 and Bundgaard No. 2 fail to compensate for the deficiences in the Karjalainen et al. references because they fail to provide a reason to modify the compounds in the Karjalainen et al. references. Aungst et al. teach

alkyl esters (such as a pivaloyl group) of a hydroxy containing pharmaceutically active compound. The Bundgaard references teach the motivation to prepare esters (also known as prodrugs) of a hydroxy containing pharmaceutically active compound. Therefore, Applicant's argument is not persuasive.

Applicant argues that Aungst et al., Bundgaard No. 1 and Bundgaard No. 2 teach away from Huhtala et al. {WO '472} because Huhtala et al. do not consider any potential ester derivatives to be prodrugs, which are inactive. In response, it is disagreed that Huhtala et al. do not contemplate potential ester derivatives to be prodrugs. The "free form" that is discussed by Huhtala et al. is the hydroxy form in which the ester form converts once the ester form is administered without the loss of the hydroxy form's pharmaceutical properties (page 8, last full paragraph).

Applicant argues that Aungst et al. disclose that the pivaloyl group is less effective as a prodrug

group. Further, Applicant argues that Aungst et al. and the Bundgaard documents highlight the unpredictability of selecting a suitable prodrug. In response, although the compound having the pivaloyl group in Aungst et al. did not hydrolyze as well as some of the other compounds in Table 1 in column 11, the pivaloyl compound did hydrolyze and no bitter taste was determined, which was the goal of the patent. Additionally, Bundgaard No. 1 indicates (page 444, second column) that sometimes the esters are not sufficiently labile *in vivo* to ensure a sufficiently high rate and extent of prodrug conversion. However, the Bundgaard references do not teach that none or very few or most esters would not be useful as prodrugs. For all the reasons given above, the rejection is deemed proper and therefore, the rejection is maintained.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura L. Stockton whose telephone number is (571) 272-0710. The examiner can normally be reached on Monday-Friday from 6:15 am to 2:45 pm. If the examiner is out of the Office, the examiner's supervisor, Joseph McKane, can be reached on (571) 272-0699.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

The Official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

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October 19, 2009